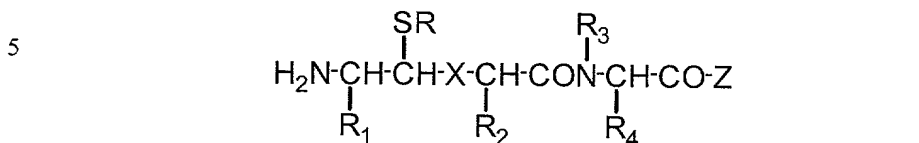


US CLAIMS

1. A compound of general formula I :



wherein :

• R₁ denotes an alkyl, alkenyl or alkynyl chain, or a cycloalkyl or
10 (cycloalkyl)alkyl group substituted by at least one

— -COOH group, optionally esterified by an alkyl group comprising
2 to 12 carbon atoms,

— SO₃H group, optionally protected by a pentyl group,

— PO₃H₂ group, optionally substituted by a
15 (-CH₂CH₂SCOR₅) group, with R₅ representing a C₁-C₄ alkyl group, a phenyl
or benzyl group, or

— tetrazolyl group.

• R₂ denotes an alkyl chain, or an aryl, arylalkyl, cycloalkyl,
(cycloalkyl)alkyl, (heteroaryl)alkyl group which may or may not be substituted
20 by at least one OH, OR, SR', NH₂, NHR', guanidiny, COOH or CONH₂ group,
or a halogen atom selected from among F, Cl, Br or I with R' representing a
straight-chain or branched C₁₋₄ alkyl group.

• R₃ denotes a hydrogen atom or a methyl group,

• R₄ denotes

25 — an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl,
(heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted
by at least one CONH₂, SO₃H, SO₂NH₂, PO₃H₂ or tetrazolyl group, with the
groups SO₃H and PO₃H₂ optionally protected,

— a C₂₋₆ alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl,
30 (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted

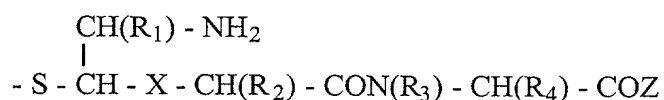
by at least one CO₂H group optionally protected, or

- R₃ and R₄ may together constitute a 5- or 6-membered heterocyclic compound, substituted by at least one CO₂H, CONH₂, SO₃H, SO₂NH₂ or PO₃H₂ group with the groups CO₂H, SO₃H and PO₃H₂ optionally protected,

5 • X denotes a group CONH or CH₂NH,

 • Z denotes a group OH, OCH₂-C₆H₅ or NR["]R^{"'} wherein R["] and R^{"'} independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, where R["] and R^{"'} may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second
10 heteroatom selected from among O, S and N, and

- R denotes a hydrogen atom or a group of formula II



II

corresponding to the symmetric disulphide of the inhibitor wherein R₁, R₂, R₃, R₄, X and Z are as hereinbefore defined,
15 and the derivatives thereof.

2. The compound according to claim 1, wherein :

- R₄ denotes an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl
20 group substituted by at least one CONH₂, SO₃H, SO₂NH₂, PO₃H₂ or tetrazolyl group, with the groups SO₃H and PO₃H₂ optionally being protected as described above, or

- R₄ constitutes with R₃ a 5- or 6-membered heterocyclic compound, substituted by at least one CO₂H, CONH₂, SO₃H, SO₂NH₂ or PO₃H₂ group
25 with the groups CO₂H, SO₃H and PO₃H₂ optionally being protected.

3. The compound according to claim 1, wherein R_4 and R_3 together constitute a 5- or 6-membered, heterocyclic compound substituted by at least one group CO_2H , CONH_2 , SO_3H , SO_2NH_2 or PO_3H_2 with the groups CO_2H , SO_3H and PO_3H_2 optionally being protected.

5

4. The compound according to claim 1, wherein X denotes a CONH function.

5. The compound according to claim 1, wherein R_2 denotes an optionally substituted alkyl or arylalkyl chain.

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6. The compound according to claim 1, which is selected from the group consisting in :

N-[[[(2S,3R)- and (2R,3R)-3-amino-2-mercapto-5-sulphonate] pentanoyl]-L.Tyr-L.Sal-OH ;

15

N-[[[(2S,3R)- and (2R,3R)-3-amino-2-mercapto-5-sulphonate] pentanoyl]-L.Tyr-L.hSal-OH ;

N-[[[(2S,3R)- and (2R,3R)-3-amino-5-carboxy-2-mercapto] pentanoyl]-L.Ile-L.(3R)(3-COOH)Pro-OH ;

20

N-[[[(2S,3R)- and (2R,3R)-3-amino-5-phosphonate-2-mercapto] pentanoyl]-L.Ile-L.Glu-OH ;

the N-[[[(2S,3R) and (2R,3R), 3-amino-2-mercapto-5-sulphonate] pentanoyl]-L.Ile-L.Sal-OH ;

N-[[[(2S,3R)- and (2R,3R)-3-amino-2-mercapto-5-sulphonate] pentanoyl]-L.Ile-L.(3R)(3-COOH)Pro-OH ;

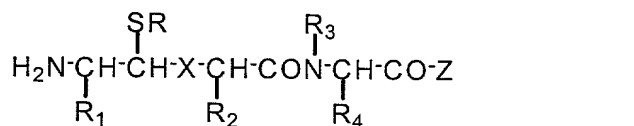
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N-[[[(2S,3R)- and (2R,3R)-3-amino-2-mercapto-5-sulphonate] pentanoyl]-L.Ile-L.(3S)(3-COOH)Pro-OH ; and

N-[[[(2S,3R)- and (2R,3R)-3-amino-2-mercapto-5-sulphonate] pentanoyl]-L.Ile-L.Glu-NH₂.

T002207-2680660

7. A process for preparing a compound of general formula I



wherein

- R_1 denotes an alkyl, alkenyl or alkynyl chain, or a cycloalkyl or (cycloalkyl)alkyl group substituted by at least one

- $-\text{COOH}$ group, optionally esterified by an alkyl group comprising 2 to 12 carbon atoms,

- SO_3H group, optionally protected by a pentyl group,

- PO_3H_2 group, optionally substituted by a $(-\text{CH}_2\text{CH}_2\text{SCOR}_5)$ group, with R_5 representing a $\text{C}_1\text{-C}_4$ alkyl group, a phenyl or benzyl group, or

- tetrazolyl group.

- R_2 denotes an alkyl chain, or an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl group which may or may not be substituted by at least one OH, OR, SR' , NH_2 , NHR' , guanidiny, COOH or CONH_2 group, or a halogen atom selected from among F, Cl, Br or I with R' representing a straight-chain or branched C_{1-4} alkyl group.

- R_3 denotes a hydrogen atom or a methyl group,

- R_4 denotes

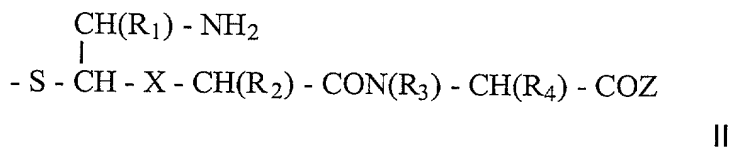
- an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one CONH_2 , SO_3H , SO_2NH_2 , PO_3H_2 or tetrazolyl group, with the groups SO_3H and PO_3H_2 optionally protected,

- a C_{2-6} alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one CO_2H group optionally protected, or

- R_3 and R_4 may together constitute a 5- or 6-membered heterocyclic compound, substituted by at least one CO_2H , CONH_2 , SO_3H , SO_2NH_2 or

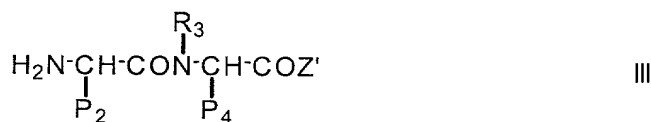
PO₃H₂ group with the groups CO₂H, SO₃H and PO₃H₂ optionally protected,

- X denotes a group CONH,
- Z denotes a group OH, OCH₂-C₆H₅ or NR''R''' wherein R'' and R''' independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, where R'' and R''' may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second heteroatom selected from among O, S and N, and
- R denotes a hydrogen atom or a group of formula II



corresponding to the symmetric disulphide of the inhibitor wherein R₁, R₂, R₃, R₄, X and Z are as hereinbefore defined,

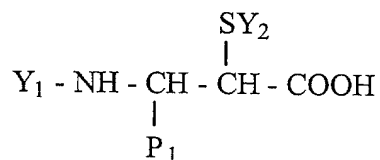
which involves at least coupling an ester dipeptide of general formula III



wherein

- P₂ and P₄ correspond to protected forms of R₂ and R₄,
- Z' denotes an OC(CH₃)₃, OCH₂-C₆H₅ or NR''R''' group wherein R'' and R''' independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, while R'' and R''' may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second heteroatom selected from among O, S and N,

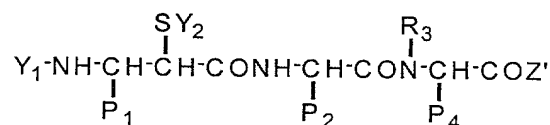
with a compound of general formula IV



IV

wherein :

- Y_1 denotes a protecting group
- Y_2 denotes a protecting group and
- P_1 denotes a protected form of R_1 ,
under conditions suitable to produce compound V



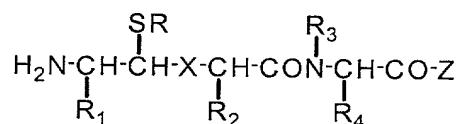
V

and deprotecting it for obtaining said compound of general formula I.

8. The process according to claim 7, wherein the coupling reaction is carried out in an organic solvent in the presence of a coupling agent and a tertiary amine and at a temperature of the order of 20°C.

9. A process according to claim 7, wherein the two asymmetric carbons of the dipeptide ester of general formula III have an S configuration.

10. A process for preparing a compound of general formula I



I

wherein :

- R_1 denotes an alkyl, alkenyl or alkynyl chain, or a cycloalkyl or

- -COOH group, optionally esterified by an alkyl group comprising 2 to 12 carbon atoms,

— PO₃H₂ group, optionally substituted by a (-CH₂CH₂SCOR₅) group, with R₅ representing a C₁-C₄ alkyl group, a phenyl or benzyl group, or

- R₂ denotes an alkyl chain, or an aryl, arylalkyl, cycloalkyl,

- R₃ denotes a hydrogen atom or a methyl group,

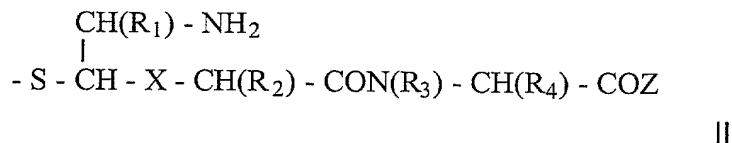
— an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (aryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted with at least one CONH₂, SO₃H, SO₂NH₂, PO₃H₂ or tetrazolyl group, with the SO₃H and PO₃H₂ optionally protected,

• R₃ and R₄ may together constitute a 5- or 6-membered heterocyclic compound, substituted by at least one CO₂H, CONH₂, SO₃H, SO₂NH₂ or PO₃H₂ group with the groups CO₂H, SO₃H and PO₃H₂ optionally protected,

• Z denotes a group OH, OCH₂-C₆H₅ or NR^{''}R^{'''} wherein R^{''} and R^{'''} independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, where R^{''} and R^{'''} may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second

heteroatom selected from among O, S and N, and

- R denotes a hydrogen atom or a group of formula II

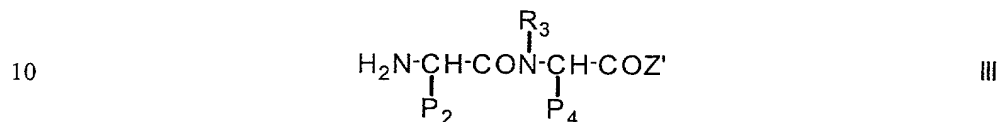


5

corresponding to the symmetric disulphide of the inhibitor wherein R₁, R₂, R₃, R₄, X and Z are as hereinbefore defined,

which involves at least :

- condensing a compound of general formula III



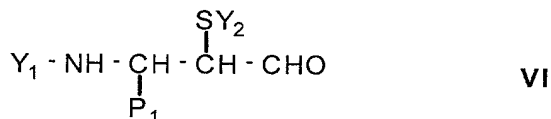
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wherein Z' denotes an OC(CH₃)₃, OCH₂-C₆H₅ or NR''R''' group with R'' and R''' independently of one another may denoting a hydrogen atom or an alkyl, aryl or arylalkyl group, where R'' and R''' may, together with the nitrogen atom, constitute a 5- or 6-membered heterocycle possibly having a second

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heteroatom selected from among O, S and N,
with a compound of general formula VI,

20

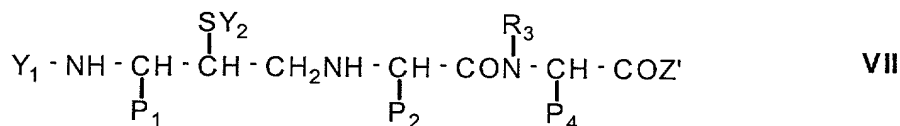


wherein :

- Y₁ denotes a protecting group
- Y₂ denotes a protecting group and
- P₁ denotes a protected form of R₁,

25

- reducing the intermediate thus formed to produce the compound of general formula VII

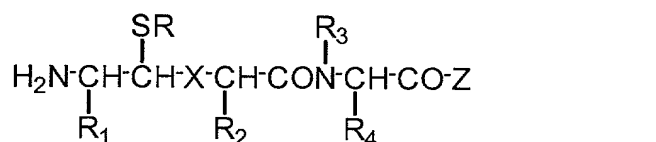


5 by deprotecting the so-obtained compound and obtaining said compound of general formula I.

11. A process according to claim 9, wherein the two asymmetric carbons of the dipeptide ester of general formula III have an S configuration.

10

12. Use of a compound of formula (I) :



15

wherein :

- R₁ denotes an alkyl, alkenyl or alkynyl chain, or a cycloalkyl or (cycloalkyl)alkyl group substituted by at least one

- -COOH group, optionally esterified by an alkyl group comprising 2 to 12 carbon atoms,

20

- SO₃H group, optionally protected by a pentyl group,

- PO₃H₂ group, optionally substituted by a (-CH₂CH₂SCOR₅) group, with R₅ representing a C₁-C₄ alkyl group, a phenyl or benzyl group, or

- 25 – tetrazolyl group.

- R₂ denotes an alkyl chain, or an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl group which may or may not be substituted by at least one OH, OR, SR', NH₂, NHR', guanidiny, COOH or CONH₂ group, or a halogen atom selected from among F, Cl, Br or I with R' representing a

30

- straight-chain or branched C₁₋₄ alkyl group.

• R₃ denotes a hydrogen atom or a methyl group,

• R₄ denotes

– an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one CONH₂, SO₃H, SO₂NH₂, PO₃H₂ or tetrazolyl group, with the groups SO₃H and PO₃H₂ optionally protected,

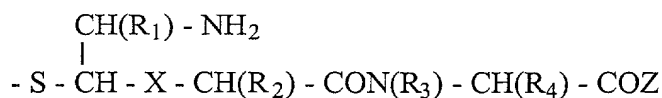
– a C₂₋₆ alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one CO₂H group optionally protected, or

• R₃ and R₄ may together constitute a 5- or 6-membered heterocyclic compound, substituted by at least one CO₂H, CONH₂, SO₃H, SO₂NH₂ or PO₃H₂ group with the groups CO₂H, SO₃H and PO₃H₂ optionally protected,

• X denotes a group CONH or CH₂NH,

• Z denotes a group OH, OCH₂-C₆H₅ or NR''R''' wherein R'' and R''' independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, where R'' and R''' may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second heteroatom selected from among O, S and N, and

• R denotes a hydrogen atom or a group of formula II



II

corresponding to the symmetric disulphide of the inhibitor wherein R₁, R₂, R₃, R₄, X and Z are as hereinbefore defined,

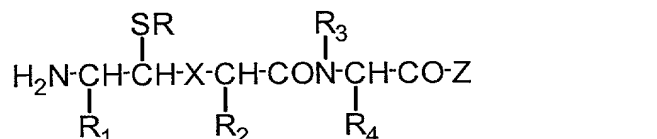
and the derivatives thereof,

as a selective inhibitor of aminopeptidase A.

13. Use according to claim 12 for preparing a medicament intended to reduce food intake, modulate anxiety states or panic attacks or treat essential

and secondary arterial hypertension, cardiac and renal failure, disorders of hydrodynamic homeostasis, myocardial infarct and proteinuria in diabetics.

14. Pharmaceutical composition containing as active ingredient at least one compound of general formula (I) :



wherein :

- R₁ denotes an alkyl, alkenyl or alkynyl chain, or a cycloalkyl or (cycloalkyl)alkyl group substituted by at least one
 - -COOH group, optionally esterified by an alkyl group comprising 2 to 12 carbon atoms,
 - SO₃H group, optionally protected by a pentyly group,
 - PO₃H₂ group, optionally substituted by a (-CH₂CH₂SCOR₅) group, with R₅ representing a C₁-C₄ alkyl group, a phenyl or benzyl group, or
 - tetrazolyl group.
- R₂ denotes an alkyl chain, or an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl group which may or may not be substituted by at least one OH, OR, SR', NH₂, NHR', guanidinylyl, COOH or CONH₂ group, or a halogen atom selected from among F, Cl, Br or I with R' representing a straight-chain or branched C₁₋₄ alkyl group.
- R₃ denotes a hydrogen atom or a methyl group,
- R₄ denotes
 - an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one CONH₂, SO₃H, SO₂NH₂, PO₃H₂ or tetrazolyl group, with the groups SO₃H and PO₃H₂ optionally protected,

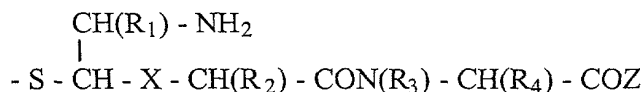
– a C₂₋₆ alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one CO₂H group optionally protected, or

• R₃ and R₄ may together constitute a 5- or 6-membered heterocyclic compound, substituted by at least one CO₂H, CONH₂, SO₃H, SO₂NH₂ or PO₃H₂ group with the groups CO₂H, SO₃H and PO₃H₂ optionally protected,

• X denotes a group CONH or CH₂NH,

• Z denotes a group OH, OCH₂-C₆H₅ or NR''R''' wherein R'' and R''' independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, where R'' and R''' may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second heteroatom selected from among O, S and N, and

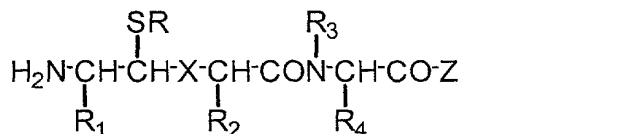
• R denotes a hydrogen atom or a group of formula II



II

corresponding to the symmetric disulphide of the inhibitor wherein R₁, R₂, R₃, R₄, X and Z are as hereinbefore defined, and the derivatives thereof.

15. Diagnostic system for detecting and titrating aminopeptidase A, characterised in that it contains at least one compound of general formula (I):



wherein :

• R₁ denotes an alkyl, alkenyl or alkynyl chain, or a cycloalkyl or (cycloalkyl)alkyl group substituted by at least one

- -COOH group, optionally esterified by an alkyl group comprising 2 to 12 carbon atoms,
- SO_3H group, optionally protected by a pentyl group,
- PO_3H_2 group, optionally substituted by a
 5 $(\text{-CH}_2\text{CH}_2\text{SCOR}_5)$ group, with R_5 representing a $\text{C}_1\text{-C}_4$ alkyl group, a phenyl or benzyl group, or
- tetrazolyl group.

- R_2 denotes an alkyl chain, or an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl group which may or may not be substituted
 10 by at least one OH , OR , SR' , NH_2 , NHR' , guanidiny, COOH or CONH_2 group, or a halogen atom selected from among F , Cl , Br or I with R' representing a straight-chain or branched C_{1-4} alkyl group.

- R_3 denotes a hydrogen atom or a methyl group,

- R_4 denotes

- an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted
 15 by at least one CONH_2 , SO_3H , SO_2NH_2 , PO_3H_2 or tetrazolyl group, with the groups SO_3H and PO_3H_2 optionally protected,

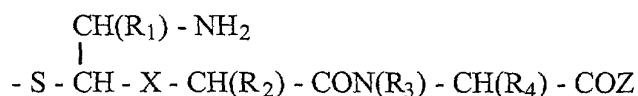
- a C_{2-6} alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted
 20 by at least one CO_2H group optionally protected, or

- R_3 and R_4 may together constitute a 5- or 6-membered heterocyclic compound, substituted by at least one CO_2H , CONH_2 , SO_3H , SO_2NH_2 or PO_3H_2 group with the groups CO_2H , SO_3H and PO_3H_2 optionally protected,

- X denotes a group CONH or CH_2NH ,

- Z denotes a group OH , $\text{OCH}_2\text{-C}_6\text{H}_5$ or $\text{NR}''\text{R}'''$ wherein R'' and R''' independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, where R'' and R''' may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second
 25
 30 heteroatom selected from among O , S and N , and

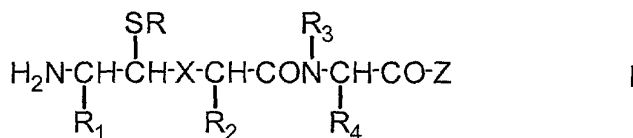
- R denotes a hydrogen atom or a group of formula II



II

corresponding to the symmetric disulphide of the inhibitor wherein R₁, R₂, R₃, R₄, X and Z are as hereinbefore defined, and the derivatives thereof.

16. A method for the prevention or treatment of anxiety states or panic attacks, essential and secondary arterial hypertension, cardiac and renal failure, disorders of hydrodynamic homeostasis, myocardial infarct and proteinuria in diabetics, comprising administering to a patient in need of such treatment a therapeutically efficient amount of a compound of general formula (I) :



wherein :

- R₁ denotes an alkyl, alkenyl or alkynyl chain, or a cycloalkyl or (cycloalkyl)alkyl group substituted by at least one
 - -COOH group, optionally esterified by an alkyl group comprising 2 to 12 carbon atoms,
 - SO₃H group, optionally protected by a pentyl group,
 - PO₃H₂ group, optionally substituted by a (-CH₂CH₂SCOR₅) group, with R₅ representing a C₁-C₄ alkyl group, a phenyl or benzyl group, or
 - tetrazolyl group.

• R_2 denotes an alkyl chain, or an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl group which may or may not be substituted by at least one OH, OR, SR', NH₂, NHR', guanidiny, COOH or CONH₂ group, or a halogen atom selected from among F, Cl, Br or I with R' representing a straight-chain or branched C₁₋₄ alkyl group.

• R_3 denotes a hydrogen atom or a methyl group,

• R_4 denotes

– an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one CONH₂, SO₃H, SO₂NH₂, PO₃H₂ or tetrazolyl group, with the groups SO₃H and PO₃H₂ optionally protected,

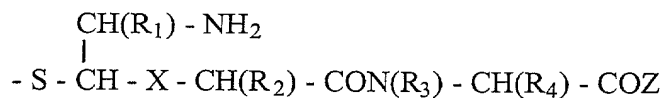
– a C₂₋₆ alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one CO₂H group optionally protected, or

• R_3 and R_4 may together constitute a 5- or 6-membered heterocyclic compound, substituted by at least one CO₂H, CONH₂, SO₃H, SO₂NH₂ or PO₃H₂ group with the groups CO₂H, SO₃H and PO₃H₂ optionally protected,

• X denotes a group CONH or CH₂NH,

• Z denotes a group OH, OCH₂-C₆H₅ or NR''R''' wherein R'' and R''' independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, where R'' and R''' may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second heteroatom selected from among O, S and N, and

• R denotes a hydrogen atom or a group of formula II

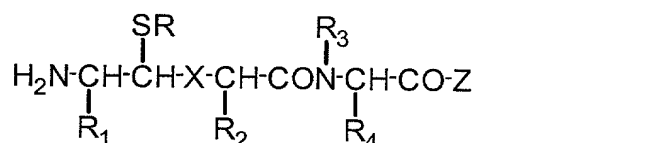


II

corresponding to the symmetric disulphide of the inhibitor wherein R₁, R₂, R₃, R₄, X and Z are as hereinbefore defined,

and the derivatives thereof.

17. A method of diagnosis of anxiety states or panic attacks, essential and secondary arterial hypertension, cardiac and renal failure, disorders of hydrodynamic homeostasis, myocardial infarct and proteinuria in diabetics, wherein the aminopeptidase A is evaluated in a biological sample of a patient to be tested by using a compound of formula (I) :



wherein :

- R₁ denotes an alkyl, alkenyl or alkynyl chain, or a cycloalkyl or (cycloalkyl)alkyl group substituted by at least one

- -COOH group, optionally esterified by an alkyl group comprising 2 to 12 carbon atoms,
- SO₃H group, optionally protected by a pentyl group,
- PO₃H₂ group, optionally substituted by a (-CH₂CH₂SCOR₅) group, with R₅ representing a C₁-C₄ alkyl group, a phenyl or benzyl group, or
- tetrazolyl group.

- R₂ denotes an alkyl chain, or an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl group which may or may not be substituted by at least one OH, OR, SR', NH₂, NHR', guanidiny, COOH or CONH₂ group, or a halogen atom selected from among F, Cl, Br or I with R' representing a straight-chain or branched C₁₋₄ alkyl group.

- R₃ denotes a hydrogen atom or a methyl group,

- R₄ denotes

- an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted

by at least one CONH_2 , SO_3H , SO_2NH_2 , PO_3H_2 or tetrazolyl group, with the groups SO_3H and PO_3H_2 optionally protected,

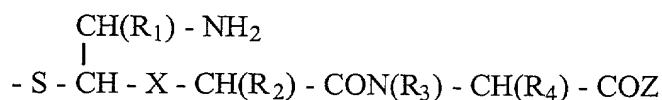
– a C_{2-6} alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted
5 by at least one CO_2H group optionally protected, or

- R_3 and R_4 may together constitute a 5- or 6-membered heterocyclic compound, substituted by at least one CO_2H , CONH_2 , SO_3H , SO_2NH_2 or PO_3H_2 group with the groups CO_2H , SO_3H and PO_3H_2 optionally protected,

- X denotes a group CONH or CH_2NH ,

10 • Z denotes a group OH , $\text{OCH}_2\text{-C}_6\text{H}_5$ or $\text{NR}''\text{R}'''$ wherein R'' and R''' independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, where R'' and R''' may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second heteroatom selected from among O, S and N, and

15 • R denotes a hydrogen atom or a group of formula II



II

corresponding to the symmetric disulphide of the inhibitor wherein R_1 ,
20 R_2 , R_3 , R_4 , X and Z are as hereinbefore defined,

and the derivatives thereof,

and is compared to the level present in normal subjects.